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ORIGINAL PAPER

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Persistence and change of PTSD symptomatology

A longitudinal co-twin control analysis of the Vietnam Era Twin Registry

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Abstract *Introduction* Previous twin studies have demonstrated a strong association between the degree of combat exposure and PTSD, and the continued presence of PTSD, almost two decades after combat. Independent genetic effects have also been demonstrated for both combat exposure and PTSD vulnerability in Vietnam veterans. The current study, involving a subset of male-male twin pairs discordant for service in Southeast Asia (SEA), is a follow-up to an earlier study conducted in 1987. The purpose of this study is to examine the changes in the combat exposure-PTSD relationship over an additional decade of time. *Methods* The Mississippi Scale for Combat-Related or Civilian PTSD was administered by telephone in 1997 during a follow-up survey of the Vietnam Era Twin Registry. Only twins discordant for service in Southeast Asia who originally participated in the 1987 study were included. Results of this scale and the original 1987 PTSD symptom scale were separately standardized using z-score transformations and used as dependent variables in a random effects regression model with zygosity, time and combat exposure as independent variables. Main effects and interactions were estimated to address whether there were differential effects of combat on PTSD over time, and whether there was evidence of genetic covariation between combat exposure and PTSD in 1987 that persisted to 1997. *Results* Combat exposure was strongly associated with PTSD in both 1987 and 1997. Although still highly significant, the effect sharply diminished over time. There is little evidence for a shared genetic vulnerability between combat and PTSD in either 1987 or 1997. *Conclusion* This analysis documents the continuing role of combat exposure (i. e., trauma severity) on the persistence and chronicity of PTSD. Nearly 25 years after the end of hostilities, PTSD symptoms continue to be elevated in those exposed to the highest levels of combat. There is no evidence that genetic influences on exposure to combat are shared with those inducing a genetic vulnerability to PTSD. Clinicians need to be aware of the persistent and long-term residual effects of trauma exposure

Key words PTSD – genetics – twins – combat

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Introduction

Post Traumatic Stress Disorder (PTSD) in both combat veterans and civilians is a dynamic product of exposure to trauma (by diagnostic definition), the severity of the

trauma (Pynoos et al. 1987; Goldberg et al. 1990; Green et al. 1990), and underlying familial/genetic vulnerability (Breslau et al. 1991; Davidson et al. 1991; True et al. 1993). Studies of Vietnam era veteran twin pairs have helped to clarify the relative contributions of genetic and environmental influences to the pathogenesis of PTSD. Co-twin control studies in monozygotic (MZ) twins have demonstrated a strong association between the severity of combat exposure and PTSD (Goldberg et al. 1990). Classical twin studies involving MZ and dizygotic (DZ) Vietnam era veteran twins have found evidence supporting a genetic contribution to service in Southeast Asia and more specifically to the severity of combat exposure (Lyons et al. 1993). These findings suggest what has been termed "genetic control of exposure to the environment" (Kendler and Eaves 1986). Further, these studies have demonstrated a genetic vulnerability to PTSD symptoms that is independent of the effects of combat exposure and the genetic influences on that exposure (True et al. 1993).

The above-noted independence of genetic effects on PTSD vulnerability and combat exposure was based on a cross-sectional twin study of PTSD symptoms performed more than a decade after military service in Vietnam. Because the behavioral effects of genes can change over the life cycle (Lyons et al. 1995), it remains unknown to what extent these relationships would change over time.

The present study examines the persistence and change of PTSD symptoms in a population-based sample of veterans. Using twins from the Vietnam Era Twin Registry, a longitudinal co-twin control study was conducted that assessed PTSD symptoms at two points a decade apart (1987 and 1997). With these data, we address three questions: Do symptoms of PTSD persist over longer periods of time? Is the strength of the combat exposure-PTSD association maintained over time? Does the lack of overlap between the genes that influence exposure to combat and vulnerability to PTSD (i. e., the absence of "genetic co-variation") change over time?

Subjects and methods

The Vietnam Era Twin Registry

The Vietnam Era Twin (VET) Registry is one of the only national registries of twins in the US (Goldberg et al. 2002). The VET Registry was assembled from computerized records maintained by the Department of Defense (DoD), supplemented with data from Veterans Affairs (VA) computer files. A computerized record linkage methodology was developed that identified pairs of records that had a reasonable probability of being twins. The algorithm that was used involved the following criteria: males, born between 1939 and 1957, served on active duty during the Vietnam era (the interval 1965–1975), same last name, different first name, same date of birth, and similar Social Security numbers. Possible twins were identified from review of the hardcopy military records and twinship was subsequently confirmed for approximately 7.500 twins.

Survey data collection

In 1987, a 24-page survey was mailed to all twin pairs; after three waves of mailing, telephone follow-up was initiated. The survey collected a broad spectrum of health measures and assigned zygosity (Eisen et al. 1989) from responses to twin similarity questions. In total, 10.979 individuals responded to the mail and telephone survey for a 74% response rate; the pairwise response rate for twins was 64%, representing 4.774 pairs. Of the responding pairs, slightly more than 53% were monozygotic and 44% were dizygotic. Zygosity could not be assigned in 3% of the pairs.

In the 1987 survey, all twins were asked about their service in Southeast Asia. Based on this question, we identified 922 pairs where both twins served in SEA, 1,976 pairs where neither twin served in SEA, and 1,728 pairs where one twin served in SEA and the other twins served elsewhere. Combat exposure was assessed in those individuals who reported serving in SEA by asking each a series of 18 questions about specific military experiences (Goldberg et al. 1990). An ordinal index of combat exposure was created from these items (SEA service with no combat, and SEA service with low, medium, and high combat); this index was validated against combat-related medals and has good internal and test-retest reliability (Janes et al. 1991).

In 1997, a telephone follow-up survey of all twins who were discordant for SEA service was undertaken in preparation for a study of the origin of psychophysiologic abnormalities in PTSD (Orr et al. 2003). Out of the 1,728 SEA discordant twins identified in 1987, a total of 696 twin pairs both responded to the 1997 survey and provided complete data. These 696 pairs represent the analytic sample for the present study. Respondents to the 1997 survey were no different than non-respondents for SEA service and zygosity; however, non-respondents were significantly ($p < 0.001$) more likely to be older, served in combat and experienced symptoms of PTSD.

Assessment of PTSD symptoms

Fifteen question items in the 1987 survey collected information on PTSD symptoms (True et al. 1993). The items broadly correspond to the criteria specified in the DSM-III-R definition of PTSD and include symptoms relating to re-experiencing, avoidance and increased arousal. Twins were asked to indicate the frequency of symptoms (very often, often, sometimes, almost never, never) during the preceding 6 months. The PTSD symptom questions were asked with reference to "your time in the military" so that twins who did not serve in Southeast Asia could also respond. In the 1997 telephone survey, PTSD symptoms were measured using the Mississippi PTSD symptom scale (Keane et al. 1988); a civilian version of the items was administered to those who did not serve in SEA (Keane et al. 1988). This 35-item, 5-point Likert, self-report scale has high internal consistency, test-retest reliability, convergent validity (with the SCID interview) and discriminant validity for identifying veterans with and without PTSD (Keane et al. 1988).

PTSD symptom scale construction

From the 1987 PTSD symptoms, we constructed an overall score by summing the item responses across all 15 questions. Scores ranged from 15 to 75 with a mean of 26.2 (s. d. = 10.2) and a median of 24. Cronbach's alpha for the 1987 PTSD symptom score was 0.9 indicating a high degree of internal consistency. The same PTSD symptom questions were previously administered to a sub-sample of 150 twin pairs as part of the pilot study for the VET Registry that was conducted in 1984. From the 192 individuals who responded to both the 1984 and 1987 questionnaires, we calculated the test-retest reliability of the PTSD symptom score to be 0.6.

The Mississippi PTSD items collected in 1997 were used to create a scale by summing each of the individual items (Keane et al. 1988). The Mississippi scores ranged from 37 to 151 and had a mean of 67.6 (s. d. = 17.8); Cronbach's alpha was 0.9 indicating a high degree of internal consistency.

Statistical analysis

Initial descriptive analysis estimated mean PTSD symptom scores (along with standard deviations) in twins who served in SEA and their co-twins who did not serve in SEA. This was done for both time points and separately in MZ and DZ twins. As a prelude to the longitudinal analysis, we performed a z-transformation to construct a standard score for each twin at each time point. We used these standardized PTSD scores as the dependent variables in a random effects regression model. These models are especially well suited for co-twin control analyses (Hu et al. 1998; Quirk et al. 2001; Guo and Wang 2002) since they account for the paired structure of the data. In our longitudinal regression analysis, we included as independent variables the main effects of: zygosity, time, and combat exposure level (including non-SEA service as the reference level). We also fit a series of models to assess specific forms of interaction involving these three variables.

While the main effect of combat exposure on PTSD is fairly straightforward to model, the role of zygosity deserves more explanation. Our estimates of the combat-PTSD association are derived from within pair differences in PTSD, since in every pair one sib served in combat and the other did not. A greater association in DZ compared to MZ twin pairs (which would be evident as a significant combat exposure by zygosity interaction term) would suggest that there is a shared genetic factor influencing BOTH combat exposure and PTSD. This would imply that a genetic covariation at least in part explains the observed association between combat and PTSD. Interaction models with time permitted us to assess whether: 1) there were differential effects of combat on PTSD over time, and 2) any evidence of a complex pattern of genetic covariation between combat and PTSD that changed over time. Statistical testing was based on Wald tests for variables included in the model. We also repeated our analysis using a dichotomous indicator of PTSD symptom level; based on the standard scores, we divided the sample into a twins with high symptom levels (representing the highest quartile at each time point) or not. In these random effect logistic models, we obtained adjusted estimates of the odds ratios for combat exposure in both 1987 and 1997 using the non-SEA group as the reference. Finally, to control for the possibility of non-response bias (since only part of the original 1987 sample was accessed in 1997), we used a Heckman type of non-response adjustment (Leigh et al. 1993). This analysis incorporated the probability of non-response estimated from the 1987 PTSD scores as a covariate in the mixed effects models.

Results

Table 1 presents the mean 1987 and 1997 standardized PTSD symptom scores for those who served and did not serve in SEA according to zygosity. During each time period and for each zygosity group the scores are considerably larger in twins who served in SEA compared to those who did not. Figs. 1 and 2 present the standardized PTSD scores according to combat exposure levels in MZ and DZ twins. In 1987, there is monotonic association between combat exposure level and the PTSD symptom score, such that as combat level increases there is a sharp rise in PTSD symptoms. Twins who served in SEA but did not experience combat and those with low levels of combat experience had generally similar PTSD symptom scores to twins who did not serve in SEA. Twins with medium and high combat levels reported substantially elevated PTSD symptoms. In 1997, this pattern persisted, with those at medium and high combat continuing to have high levels of PTSD symptoms; for those who did not experience combat (the non-SEA, SEA no combat and SEA low combat groups) there was a convergence of symptom scores at a low level. The pattern in DZ pairs was generally similar (Fig. 2). Results from the random effects modeling confirm these general patterns with significant effects for both combat ($p < 0.001$) and time period ($p < 0.001$). Further, there was a significant interaction between time and combat ($p < 0.001$) attributable to a greater decline in symptomatology in the medium and high combat groups than in the non-SEA and low combat groups. There was no evidence of a combat by zygosity interaction effect ($p = 0.42$), nor was there any evidence for a more complex combat by time by zygosity interaction ($p = 0.33$). Incorporation of the probability of non-response as a covariate in these models gave identical results (there was no difference in the estimated effects of combat on PTSD).

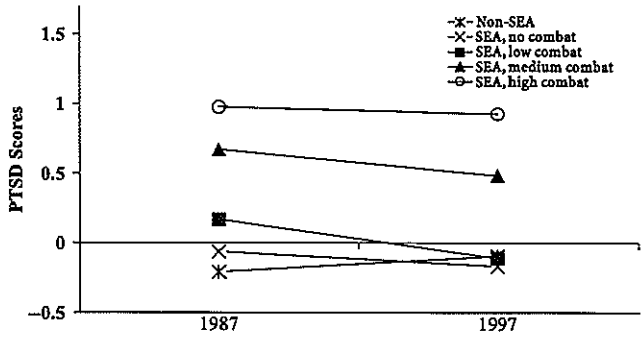

Fig. 1 MZ means for PTSD scores by combat exposure 1987 and 1997

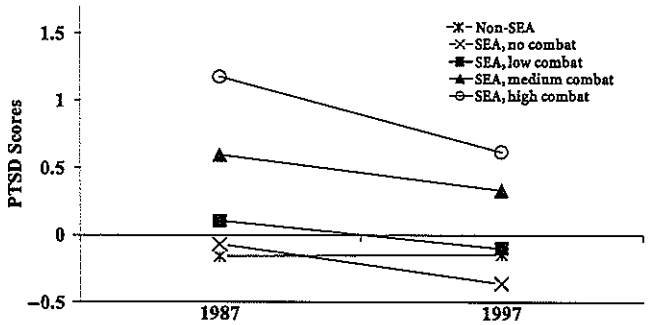

Fig. 2 DZ means for PTSD scores by combat exposure 1987 and 1997

Table 1 Mean standardized PTSD symptom scores in Vietnam Era Twin Registry pairs (mean ± s. d.) according to Southeast Asia (SEA) service and zygosity

	1987		1997	
Zygosity	Served in SEA	Did not serve in SEA	Served in SEA	Did not serve in SEA
Monozygotic (n = 361)	0.43 ± 1.13	−0.21 ± 0.81	0.26 ± 1.17	−0.09 ± 0.85
Dizygotic (n = 335)	0.45 ± 1.13	−0.16 ± 0.77	0.15 ± 1.13	−0.15 ± 0.78

Figs. 3 and 4 present odds ratios for combat level and time period estimated from the random effects logistic regression model in MZ and DZ twins. For MZ twins in 1987, there are markedly increased odds ratios for twins at medium (OR = 10) and high (OR = 15) combat exposure compared to their co-twins who did not serve in SEA. This pattern persists in 1997, although there is a marked diminution of the odds ratios at all levels of combat exposure. Nevertheless, those at the highest combat levels in 1997 still have more than a nine-fold increase in the odds of having high PTSD symptoms compared with their co-twin who did not serve in SEA. A similar general pattern of combat effects is observed for DZ twins; in 1987, the twins exposed to the highest levels of combat were at eight times greater risk of PTSD symptoms and this fell to four times in 1997. Those DZ twins who experienced lower levels of combat exposure display only a modest association with the dichotomous indicator of PTSD symptoms in both 1987 and 1997. Statistical testing found strong evidence for the effect of combat ($p < 0.001$) and time period ($p < 0.001$) and interaction of combat by time ($p < 0.05$). There was no evidence of combat by zygosity interaction ($p = 0.29$) or combat by time by zygosity ($p = 0.98$).

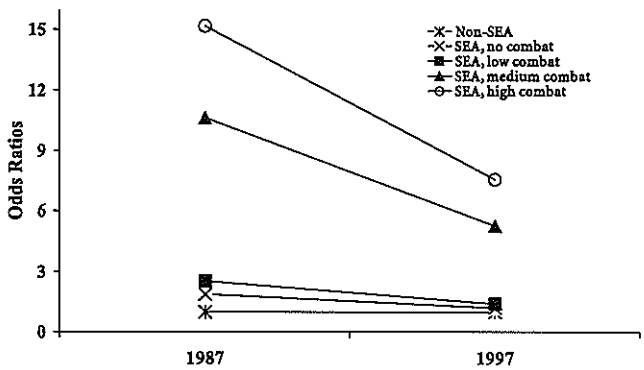

Fig. 3 MZ odds ratios for PTSD and combat exposure 1987 and 1997

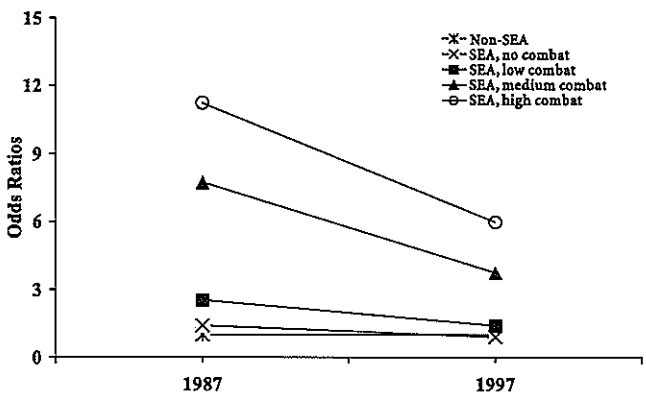

Fig. 4 DZ odds ratios for PTSD and combat exposure 1987 and 1997

Discussion

These findings clearly indicate that PTSD symptoms persist over long periods of time in this cohort of Vietnam-era veterans, although there appears to be some diminution in symptoms at the later time point. While we do not have any evidence in the 1997 sample of functional status, in the 1987 sample there was a strong relationship between PTSD symptoms and functional impairment (unpublished observations) suggesting that symptom reports in this sample have important functional consequences. The relationship between the severity of combat exposure and PTSD continues to persist, albeit with reduced strength, so that the decrease in PTSD symptoms over time appears to be greater for veterans originally exposed to higher levels of combat. There does not appear to be any evidence of genetic covariation between combat exposure and PTSD vulnerability at either time period (i. e., no combat by zygosity interaction). This latter analysis replicates, using a different method, the findings of the earlier cross-sectional analysis based on the 1987 PTSD measures suggesting that the genetic influences on combat exposure are distinct from those responsible for vulnerability to develop PTSD.

The long-term outcome of PTSD and the risk factors associated with persistence versus recovery have been incompletely investigated, particularly in population-based samples. While a number of studies have documented the chronicity of PTSD over time, most of these studies have been cross-sectional and retrospective (Breslau and Davis 1992; Kessler et al. 1995), with the few prospective studies only considering short time frames (Norris and Kaniasty 1994; Lawrence et al. 1996; Freedman et al. 1997; Udwin et al. 2000), usually one year, rarely more than three. These studies have suggested that between 30 and 50% of PTSD cases become chronic. Although fewer studies have examined risk factors for chronicity, the available evidence suggests that the rates of non-recovery are higher for life-threatening trauma such as combat or physical assault (Davidson et al. 1991), that trauma severity in combat veterans is associated with chronicity (Green et al. 1990), and that personal and familial psychiatric history are associated with non-recovery in traumatized civilian populations (Breslau and Davis 1992). The present analysis replicates with a rigorous genetic control, the continuing role of combat exposure (i. e., trauma severity) in chronicity and non-recovery from PTSD. This is consistent with aggregate PTSD data from the National Comorbidity Study project suggesting that there is little recovery or improvement after 6 years, regardless of treatment (Kessler et al. 1995). The present data show continued chronicity almost 25 years later, and document that these cases continue to be directly proportional to the degree of combat exposure. Our data cannot determine whether this persistence of symptomatology is due to veterans not accessing or following through with treat-

ment, or whether they had adequate treatment, but failed to respond.

This study has several limitations. First, the analysis was only performed on a subgroup of this population-based sample that were able to be contacted for re-screening. Comparison of respondents and non-respondents indicated significant differences for age, PTSD and combat; however, incorporating a non-response adjustment in the analysis did not alter the results. Further, our analysis used only those twin pairs who both responded in 1987 and 1997 so that within-pair differences could be assessed while controlling for genetic and familial influences. Second, two distinct measurement tools were used in 1987 and 1997, requiring that we normalize the data in order to perform the analysis. Finally, no structured diagnostic interview was done in either 1987 or 1997 so that symptom scores had to be used to infer a PTSD diagnosis. Despite these limitations, the findings are quite robust and conceptually consistent with previous findings in the field.

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